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1. Introduction

Traditionally, psychiatric research considers alcohol as a harmful substance focusing mainly on the extreme of excessive alcohol consumption. From a public health perspective, however, evaluating the effects of abstinence and moderate use of alcohol are equally important because they are much more common compared to alcohol dependence or abuse, while alcohol is incorporated in everyday nutrition of several cultures e.g. Mediterranean and South-American cultures (Room and Makela, 2000).

Several cross-sectional (Bellos et al. 2013; Caldwell et al. 2002; Kirchner et al. 2007; O'Donnell et al. 2006; Power et al. 1998; Skogen et al. 2009) and longitudinal studies (Bell and Britton, 2015; Bell and Britton, 2014; Cougle et al. 2015; Gea et al. 2013, Gea et al. 2012, Tait et al. 2012) that have examined the full range of consumption, from total abstinence to excessive use, have pointed to a possible non-linear association between alcohol use and the common mental disorders. It has been suggested that moderate levels of alcohol consumption are associated with a lower risk of mental health problems compared to total abstinence or heavy use, reflecting the analogous association of reduced mortality with moderate alcohol use (Ronksley et al. 2011). These findings are not universally accepted and have been questioned as being the result of unmeasured confounding factors or reverse causality (Bell and Britton, 2015; Holmes et al. 2014; Paljavri et al. 2009; Paschall et al. 2005; Sareen et al. 2004). Regarding the latter, the "sick-quitter" effect (Fillmore et al. 2007) could explain the increased prevalence of mental disorders in individuals abstaining from alcohol compared to moderate users (Bell and Britton, 2014), while the self-medication hypothesis (Bolton et al. 2009) may explain the association between heavy alcohol use and depression.

The above discussion is of particular interest for patients presenting in Primary Care where alcohol related problems and depression are common and often co-occur with physical health problems. Previous longitudinal studies on the association between the different levels of alcohol consumption and the common mental disorders cannot generalize their results in other cultures or clinical settings as they recruited community samples from well developed countries (Gea et al. 2013; Haynes et al. 2005; Paljavri et al. 2009; Tait et al. 2012) and assessed depression/anxiety using self-reported diagnoses (Bell and Briton, 2015; Gea et al. 2013) or generic case-finding instruments (Paljavri et al. 2009; Tait et al. 2012) that may lack clinical validity. The available primary care studies on the association between different levels of alcohol consumption and depression or anxiety are cross sectional (Bellos et al. 2013; Kirchner et al. 2007) and cannot exclude the possibility of reverse causality.

In a previous work of our research team (Bellos et al. 2013), using the cross-sectional baseline data from a WHO international study in primary health care, we found evidence for a non-linear association between the full range of alcohol use and depression or generalized anxiety disorder (GAD). Longitudinal data are also available from the same dataset in a subset of participants, who were followed-up for one year after the baseline assessment. Therefore, the aim of the current paper was to investigate the longitudinal association between different levels of alcohol consumption and a new-onset of depression or GAD in order to confirm whether the previously reported non-linear association is not the result of reverse causality.

2. Material and methods

2.1 General description of the data set

The WHO collaborative study of Psychological Problems in General Health Care (PPGHC) investigated the prevalence and associations of common mental disorders in 15 primary care centers from 14 countries worldwide (Ustun and Sartorius, 1995). The study consisted of a cross-sectional part and a one-year longitudinal extension. The cross-sectional part used a two-phase design. At the first phase, 25916 consecutive primary care attenders aged 18–65 completed the 12-item General Health Questionnaire (GHQ-12; Goldberg and Williams, 2000). For the second phase of the cross-sectional part, participants were selected using a stratified random sampling procedure according to site-specific GHQ-12 thresholds of the first phase (5438 out of 8698 eligible participants were finally assessed, 62% response rate).

Eligible for the longitudinal part of the study were all participants with a definite or subthreshold psychiatric disorder at the baseline assessment as well as a 40% random sample of the remainder. Those were asked to complete the follow-up assessment 12 months later. The response rate for the longitudinal assessment was 68.5% (n=3201). Data were collected between May 1991 and April 1992. The current paper used data from the longitudinal assessment only, while our previous paper (Bellos et al. 2013) used the cross-sectional data only.

2.2 Measures

2.2.1 Measurement of common mental disorders

The primary care version of the Composite International Diagnostic Interview (CIDI), (Wittchen et al. 1991) was used to assess the presence of depression (F32/33) and generalized anxiety disorder (GAD) (F41.1). A new onset of depression or GAD was defined in participants who met criteria of depression or GAD at follow-up but not at baseline. All disorders refer to current (one-month) morbidity.

2.2.2 Measurement of alcohol use

Alcohol use was assessed using the WHO Alcohol Use Disorders Identification Test (AUDIT), a 10-item instrument which covers recent alcohol intake, dependence and harmful use during the previous 12 months (Saunders et al. 1993). Each question is scored between 0 and 4 and the total score is ranging between 0 (total abstinence) and 40.

To take into account the possible non-linear association between alcohol use and mental disorders we used 6 groups of baseline alcohol use, including categories of abstinence or excessive drinking. The 6 groups of increasing severity were defined using the 25^{th} (abstainers), 50^{th}, 75^{th}, 90^{th} and 95^{th} percentiles of total AUDIT-score as cut-offs for all baseline participants

2.2.3 Assessment of other variables

Data on possible confounders at baseline (age, sex, marital status, years of schooling, working status, physician's rating of current physical health, self-reported presence of chronic medical illness) were recorded as described in our previous publication (Bellos et al. 2013).

2.3 Statistical Analysis

Analyses were performed with STATA/SE 10.0 (STATA Corp LP, College Station, TX). Percentages were estimated using the "survey" commands in STATA ("svy"). Weights were used to take into account the stratified sampling procedure and non- response in follow up. The association between alcohol use at baseline and a new onset of depression or GAD at follow-up was assessed with a two-level logistic regression model (level 1: individuals, level 2: primary care centres) using the "gllamm" command in STATA (Rabe-Hesketh and Skrondal, 2006). Multilevel analysis accounts for any potential clustering of data, since participants in our study were nested into 15 centres. The above models were adjusted for potential confounding variables including age, sex, marital status, years of schooling, working status, physician's rating of current physical health and self-reported chronic medical diseases as well as the presence of the other mental disorder (e.g. GAD for model where outcome was new onset-depression and depression for models of new onset-GAD) For both analyses we excluded participants with depression or GAD at baseline and the final models included 2374 and 2676 participants for studying new-onset depression and GAD as outcomes, respectively. From these models we report odds ratios (OR) and 95% confidence intervals (CI) for the increasing levels of alcohol consumption using abstainers as the reference group.

3. Results

3.1 Sample characteristics - Alcohol consumption

The 3201 primary care patients who took part at the follow-up had a mean age at baseline of 40.5 years (range: 18-65), while 62% were female. Comorbidity with a chronic medical disease was reported by 58.3% of the participants. The other baseline characteristics of the participants who took part in the follow-up were similar to those presented in our previous cross-sectional paper (Bellos et al. 2013). A new episode of depression (among participants without depression at baseline, N=2372) was reported by 4.4% of the sample and a new onset of GAD (among participants without GAD at baseline, N=2676) was reported by 3.1% of the sample, with some cross-cultural variation.

3.2 Association between baseline alcohol use and a new onset of Depression/GAD

In the crude analysis, participants with "moderate" alcohol use at baseline (audit percentiles: 51st to 90th , total audit scores 2-8) were less likely to report a new onset of depression or GAD after 1 year compared to abstainers. Excessive drinking (>95th percentile of audit scores, total audit score >12) was associated with a higher risk for a new onset of depression but not for GAD. Adjustment for confounding factors (age, sex, marital status, working status, years of education, physician's rating of physical health, self-rated presence of chronic diseases and the presence of other mental disorders in baseline) had a slight effect in the association between alcohol consumption and depression and the effect of excessive drinking became even stronger (Table 1). Regarding GAD, in the fully adjusted model (model 2, Table 1) the statistically significant lower risk for GAD was observed in upper moderate drinking (audit percentiles: 76th to 90th , audit scores: 5-8), although the trend was the same for the previous consumption category as well (audit

percentiles: 51st to 75th, audit scores: 2-4). Heavy drinking (audit percentiles: 91st to 95th) was associated (although marginally) with a higher risk for GAD. The same trend was noticed in the excessive drinking category (96th – 100th percentile), but the confidence intervals were wide and included the null value.

We also present the analysis separately for men and women (Table 2). Regarding depression, we observed the same trends as with the main analysis for both genders. However, for GAD there was a trend for an association between heavy / excessive alcohol consumption and an increased incidence of GAD in males but not in females. It should be noted that ORs were not statistically significant, possibly due to the limited statistical power.

4. Discussion

4.1 Key findings

Our results support a non-linear association between alcohol consumption and a new onset of depression and generalized anxiety disorder. In particular, participants with moderate alcohol consumption at baseline had a lower risk for developing a new onset of depression or GAD at follow-up compared to participants who abstained from alcohol at baseline. In addition, we confirmed that excessive alcohol consumption increased the risk for a new onset of depression while the association of heavy/excessive alcohol use with GAD was more complex. These findings were largely independent of the presence of chronic medical illnesses or sociodemographic variables.

4.2 Study findings under the light of the literature

Several previous cross-sectional studies, including our own analysis of the baseline data of the same WHO study (Bellos et al. 2013), have also pointed to a possible non-linear association of alcohol use with common mental disorders (Caldwell et al. 2002; O'Donnell et al. 2006; Power et al. 1998; Skogen et al. 2009). Cross-sectional studies however cannot exclude alternative explanations related to temporal issues, since common mental disorders may lead to increased alcohol consumption ["self-medication" (Bolton et al. 2009)] or alcohol use cessation ("sick-quitters"). The present longitudinal analysis confirms the results of a few other longitudinal studies on this issue (Bell and Britton, 2015; Bell and Britton, 2014; Cougle et al. 2015; Gea et al. 2013; Gea et al. 2012; Tait et al. 2012) that moderate alcohol consumption may reduce the risk for developing a new episode of depression compared to abstinence, making less likely that this is due to reverse causality. Moreover, considering the effect of physical health in alcohol mental health association

our results are in partial concordance with longitudinal studies supporting a stronger effect (Bell and Briton, 2015) but most longitudinal studies dot not specifically examined confounding due to physical health (Cougle et al. 2015; Gea et al. 2012; Tait et al. 2012). Compared to other longitudinal studies, the present study assessed mental disorders with a detailed structured psychiatric interview, used a cross-cultural sample and was conducted in Primary Care, making the generalisability of the results easier in clinical settings.

Regarding gender differences, onset of depression showed similar trends in both genders (lower risk in moderate consumption, higher in excessive consumption). This is in concordance with previous longitudinal (Gea et al. 2012, Tait et al. 2012) and cross-sectional studies (Caldwell et al. 2002; Coehlo et al. 2014; Graham et al. 2007). In GAD there was some evidence that men may be more vulnerable than women to a new onset of generalized anxiety at higher levels of alcohol consumption, although this was a non-significant trend (table 2). As most previous longitudinal studies have focused on depression only (Bell and Britton, 2014; Bulloch et al. 2012; Fergusson et al. 2009; Gea et al. 2012; Gilman and Abraham, 2001; Tait et al. 2012) this finding cannot be confirmed, but it is worth noting that some cross sectional studies do not support this distinction (Rodgers 2000; Skogen et al. 2009). In any case our subgroup analysis by gender is limited in statistical power.

The psychotropic effect of alcohol is mainly attributed to its act on GABA (gamma-aminobutyric acid) receptors, leading to relaxation, negative thoughts suppression, sedation and disinhibition, or to the opiate-mediated reward neurotransmitter systems, leading to positive reinforcement of alcohol seeking and use. These biological effects are further mediated by genetic variation within other types of neurotransmitter (serotonin) and

hormonal (corticotropin-releasing factor) systems that regulate stress and emotions (Heilig et al., 2011, Mohler et al., 2012). Moreover, the level of response to alcohol and the associated risk for developing alcohol tolerance and dependence are associated with genetic variation in GABA and serotonin receptors (Edenberg et al., 2004, Schuckit et al 1999, Soyka et al., 2008). Some longitudinal studies support the anti-oxidative properties of red wine (Vazour, 2012) and associate moderate alcohol consumption with neuroprotective effects in humans (den Heijer et al., 2004, Anstey et al., 2009) and neuroproliferation in animal models (Aberg et al., 2005) . Conclusively, a biological antidepressant and anxiolytic effect of moderate alcohol use cannot be excluded, although the exact mechanisms are largely unknown

4.3 Limitations

Our results should be considered under the following limitations: the past (pre-baseline) alcohol use and mental health history of the participants was unknown. Therefore, we cannot exclude the possibility that previous mental health problems led to abstinence ("sick quitter" effect) (Ng Fat and Shelton, 2012). Furthermore, the reported association could be explained as a result of unmeasured confounding factors such as personality, lifestyle and socioeconomic variables. We should like to note however that adjustment for several sociodemographic and physical health variables in the current study had a small effect in the reported associations. The length of follow-up in our study was relatively short (12 months) and we do not know what would happen in the longer term (Bell and Britton, 2015). Finally, in our subgroup analyses the statistical power was limited and the results should be treated with caution (type II error).

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4.4 Conclusions

Moderate daily drinking can be a slippery slope that many individuals may not be able to control (O'Keefe et al. 2007). It is difficult to predict what percentage of current moderate drinkers will face future alcohol-related problems. On the other hand, the use of alcohol to relieve affective symptoms is common among individuals with mood disorders, yet it is associated with increased psychiatric morbidity (Bolton et al. 2009). Our study points to a possible "protective" effect of moderate drinking in the risk of developing a new onset of common mental disorders. However, despite our longitudinal design, alternative explanations of unknown or unmeasured confounding factors cannot be excluded Causal inference presupposes combined and consistent evidence of a strong and “dose-response” association from different research sources, biological plausibility and randomized controlled trial evidence. Taking into account that such interventions would be unlikely or unethical to be conducted, evidence from observational studies using different but complementary methodologies (Glymour et al. 2014) could be used to conclude whether moderate alcohol consumption could lower the risk for common mental disorders. In any case, the possible beneficial effects of alcohol in mental health should be balanced against the elevated risks of excessive consumption for both physical and mental health (Lim et al. 2013).

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References

1. Åberg, E., Hofstetter, C. P., Olson, L., & Brené, S., 2005. Moderate ethanol consumption increases hippocampal cell proliferation and neurogenesis in the adult mouse. Int J Neuropsychopharmacol. 8, 557-567.
2. Anstey, K. J., Mack, H. A., Cherbuin, N., 2009. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. Am J Geriatr Psychiatry. 17, 542-555.
3. Bell, S., Britton, A., 2015. Drinking pattern during midlife and risk of developing depression during 28 years of follow-up: a prospective cohort study. Drug Alcohol Depend. 155, 111-117.
4. Bell, S., Britton, A., Kubinova, R., Malyutina, S., Pajak, A., Nikitin, Y., Bobak, M., 2014. Drinking Pattern, Abstention and Problem Drinking as Risk Factors for Depressive Symptoms: Evidence from Three Urban Eastern European Populations. PLoS ONE. 9(8).
5. Bellos, S., Skapinakis, P., Rai, D., Zitko, P., Araya, R., Lewis, G., Lionis, C., Mavreas, V., 2013. Cross-cultural patterns of the association between varying levels of alcohol consumption and the common mental disorders of depression and anxiety: Secondary analysis of the WHO Collaborative Study on Psychological Problems in General Health Care. Drug Alcohol Depend. 133, 825-831.
6. Bolton, J.M., Robinson, J., Sareen, J., 2009. Self-medication of mood disorders with alcohol and drugs in the National Epidemiologic Survey on Alcohol and Related Conditions. J Affect Disord. 115, 367-375.
7. Bulloch, A., Lavorato, D., Williams, J., Patten, S., 2012. Alcohol consumption and major depression in the general population: the critical importance of dependence. Depress Anxiety. 29, 1058-1064.
8. Caldwell, T.M., Rodgers, B., Jorm, A.F., Christensen, H., Jacomb, P.A., Korten, A.E., Lynskey, M.T., 2002. Patterns of association between alcohol consumption and symptoms of depression and anxiety in young adults. Addiction. 97, 583-94.
9. Coelho, C.L., Laranjeira, R.R., Santos, J.L., Pinsky, I., Zaleski, M., Caetano, R., Crippa, J.A.S., 2014. Depressive symptoms and alcohol correlates among Brazilians aged 14 years and older: a cross-sectional study. Subst Abuse Treat Prev Policy. 9, 29.
10. Cougle, J.R., Hakes, J.K., Macatee, R.J., Chavarria, J. Zvolensky M.J., 2015. Quality of life and risk of psychiatric disorders among regular users of Alcohol, Nicotine, and Cannabis: An analysis of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). J Psychiatr Res. 66–67, 135–141.
11. den Heijer, T., Vermeer, S. E., van Dijk, E. J., Prins, N. D., Koudstaal, P. J., van Duijn, C. M., ... Breteler, M. M., 2004. Alcohol intake in relation to brain magnetic resonance imaging findings in older persons without dementia. Am J Clin Nutr. 80, 992-997.
12. Edenberg, H. J., Dick, D. M., Xuei, X., Tian, H., Almasy, L., Bauer, L. O., ... Kwon, J., 2004. Variations in GABRA2, encoding the α2 subunit of the GABA A receptor, are associated with alcohol dependence and with brain oscillations. Am J Hum Genet.. 74, 705-714.
13. Fergusson, D.M., Boden, JM., Horwood, L.J., 2009. Tests of causal links between alcohol abuse or dependence and major depression. Archives of General Psychiatry, 66(3), 260-266.
14. Fillmore, K.M., Stockwell, T., Chikritzhs, T., Bostrom, A., Kerr, W., 2007. Moderate alcohol use and reduced mortality risk: systematic error in prospective studies and new hypotheses. Ann. Epidemiol. 17, S16-23 .
15. Gea, A., Beunza, J.J., Estruch, R., Sánchez-Villegas, A., Salas-Salvadó, J., Buil-Cosiales, P., ... & Martínez-González, M.A., 2013. Alcohol intake, wine consumption and the development of depression: the PREDIMED study. BMC medicine. 11, 192.
16. Gea, A., Martinez-Gonzalez, MA., Toledo, E., Sanchez-Villega,s A., Bes-Rastrollo, M., Nuñez-Cordoba, J.M., ... & Beunza J.J., 2012. A longitudinal assessment of alcohol intake

and incident depression: the SUN project. BMC public health. 12, 954.
17. Gilman, S.E., Abraham, H.D., 2001. A longitudinal study of the order of onset of alcohol dependence and major depression. Drug and Alcohol Dependence. 63, 277–286.
18. Glymour M., 2014. Alcohol and cardiovascular disease. BMJ. 349, g4334.
19. Goldberg, D.P., & Williams, P., 2000. General health questionnaire (GHQ). Swindon, Wiltshire, UK: nferNelson.
20. Haynes, J.C.., Farrell, M., Singleton, N., Meltzer, H., Araya, R., Lewis, G., Wiles N.J., 2005. Alcohol consumption as a risk factor for anxiety and depression: Results from the longitudinal follow-up of the National Psychiatric Morbidity Survey. BJPsych. 187, 544-551.
21. Heilig, M., Goldman, D., Berrettini, W., O'Brien C., 2011 Pharmacogenetic approaches to the treatment of alcohol addiction. Nat Rev Neurosci.. 12, 670-684.
22. Holmes, M.V., Dale, C.E., Zuccolo, L., Silverwood, R.J., Guo,,Y., Ye, Z., ... Talmud, P.J., 2014. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. BMJ. 349, g4164.
23. Kirchner, J.E., Zubritsky, C., Cody, M., Coakley, E., Chen,, H., Ware, J.H., ... Levkoff, S., 2007. Alcohol consumption among older adults in primary care. J Gen Intern Med. 22, 92-97.
24. Lim, S.S., Vos, T., Flaxman, A.D., Danaei, G., Shibuya, K., Adair-Rohani, H., ... Davis, A., 2013. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study. 2010. The lancet. 380, 2224-2260.
25. Mohler, H., 2012. The GABA system in anxiety and depression and its therapeutic potential. Neuropharmacology. 62, 42–53.
26. Ng Fat, L., Shelton, N., 2012. Associations between self-reported illness and non-drinking in young adults. Addiction. 107, 1612-1620.
27. O'Keefe, J.H., Bybee, K.A. Lavie, C.J., 2007. Alcohol and Cardiovascular Health The Razor-Sharp Double-Edged Sword. J Am Coll Cardiol. 50, 1009-1014.
28. O'Donnell, K., Wardle, J., Dantzer, C., Steptoe, A., 2006. Alcohol consumption and symptoms of depression in young adults from 20 countries. J Stud Alcohol. 67, 837-40.
29. Paljärvi, T., Koskenvuo, M., Poikolainen, K., Kauhanen, J., Sillanmäki, L., Mäkelä, P., 2009. Binge drinking and depressive symptoms: a 5-year population-based cohort study. Addiction. 104, 1168-1178.
30. Paschall, M.J., Freisthler, B., Lipton, R.I., 2005. Moderate alcohol use and depression in young adults: findings from a national longitudinal study. Am J Public Health. 95, 453-7.
31. Power, C., Rodgers, B., Hope, S., 1998. U-shaped relation for alcohol consumption and health in early adulthood and implications for mortality. The Lancet. 352(9131), 877.
32. Rabe-Hesketh, S. & Skrondal, A., 2006. Multilevel modelling of complex survey data. Journal of the Royal Statistical Society: Series A (Statistics in Society). 169, 805-827.
33. Rodgers, B., Korten, A.E., Jorm, A.F., Jacomb, P.A., Christensen, H., Henderson, A.S., 2000. Non-linear relationships in associations of depression and anxiety with alcohol use. Psychol. Med. 30, 421-32.
34. Ronksley, P.E., Brien, S.E., Turner, B.J., Mukamal, K.J., Ghali, W.A., 2011. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ. 22 (342), d671.
35. Room, R., Mäkelä, K., 2000. Typologies of the cultural position of drinking. J. Stud. Alcohol. 61, 475–483.
36. Sareen, J., McWilliams, L., Cox, B., Stein, M.B., 2004. Does a U-shaped relationship exist between alcohol use and DSM-III-R mood and anxiety disorders?. J. Affect. Disord. 82, 113–118.
37. Saunders, J.B., Aasland, O.G., Babor, T.F., De La Fuente, J.R., Grant, M., 1993.

Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption -II. Addiction. 88, 791-804.
38. Schuckit, M. A., Mazzanti, C., Smith, T. L., Ahmed, U., Radel, M., Iwata, N., Goldman, D., 1999. Selective genotyping for the role of 5-HT 2A, 5-HT 2C, and GABA α6 receptors and the serotonin transporter in the level of response to alcohol: a pilot study. Biol Psychiatry. 45, 647-651.
39. Skogen, J.C., Harvey, S.B., Henderson, M., Stordal, E., Mykletun, A., 2009. Anxiety and depression among abstainers and low-level alcohol consumers. The Nord-Trøndelag Health Study. Addiction. 104, 1519-1529.
40. Soyka, M., Preuss, U. W., Hesselbrock, V., Zill, P., Koller, G., Bondy, B., 2008. GABA-A2 receptor subunit gene (GABRA2) polymorphisms and risk for alcohol dependence. J Psychiatr Res. 42, 184-191.
41. Tait, R.J., French, D.J., Burns, R., Anstey, K.J., 2012. Alcohol use and depression from middle age to the oldest old: gender is more important than age. Int Psychogeriatr. 24, 1275-1283.
42. Ustun, T., Sartorius, N. Mental Illness in General Health Care: An International Study. London, England: John Wiley & Sons. 1995.
43. Vanzour, D., 2012. Dietary polyphenols as modulators of brain functions: biological actions and molecular mechanisms underpinning their beneficial effects. Oxid Med Cell Longev. 2012:914273
44. Wittchen, H.U., Robins, L.N., Cottler, L.B., Sartorius, N., Burke, J.D., Regier, D., 1991. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. Br J Psychiatry. 159, 645-653.

Tables

Table 1 Association between different levels of alcohol use at baseline and new onset of Depression/GAD in an international primary care sample (n=3201)

Generalized Linear Latent and Mixed Models (GLLAMM)		Incidence at one year follow-up							
		Depression (among participants free of depression at baseline, n=2372)				**GAD** (among participants free of GAD at baseline, n=2676)			
percentile range of AUDIT SCORE at baseline	*Corresponding AUDIT-score*	N (%)	Crude OR (95% CI)	Adjusted OR 1 † (95% CI)	Adjusted OR 2 ‡ (95% CI)	N (%)	Crude OR (95% CI)	Adjusted OR 1 † (95% CI)	Adjusted OR 2 ‡ (95% CI)
0 – 25th	0 (abstainers)	70 (5.7%)	**1.0**	**1.0**	**1.0**	74 (4.5%)	**1.0**	**1.0**	**1.0**
26th – 50th	1	48 (4.5%)	**0.7** (0.4 – 1.2)	**0.8** (0.5 – 1.2)	**0.8** (0.5 – 1.3)	40 (2.8%)	**0.7** (0.3 – 1.3)	**0.7** (0.3 – 1.8)	**0.8** (0.3 – 2.1)
51st - 75th	2-4	22 (2.6%)	**0.3*** (0.1 – 0.7)	**0.4*** (0.2 – 0.9)	**0.4*** (0.2 – 0.9)	26 (2.2%)	**0.5*** (0.3 – 0.8)	**0.6** (0.3 – 1.3)	**0.8** (0.4 – 1.8)
76th – 90th	5-8	21 (3%)	**0.5*** (0.3 – 0.9)	**0.9** (0.5 – 1.5)	**0.9** (0.5– 1.6)	11 (1%)	**0.2*** (0.1 – 0.4)	**0.4*** (0.2 – 0.8)	**0.4*** (0.2 – 0.9)
91st – 95th	9-12	11 (2.8%)	**0.5** (0.2 – 1.01)	**0.7** (0.4 – 1.4)	**0.8** (0.4 – 1.4)	8 (2.7%)	**0.8** (0.4 – 1.6)	**1.4** (0.9 – 2.2)	**1.6*** (1.1 – 2.3)
96th – 100th	13-34	13 (9.9%)	**2.3*** (1.01 – 4.0)	**3.5*** (1.6 – 7.7)	**3.2*** (1.4 – 7.1)	8 (4.2%)	**0.7** (0.4 – 1.5)	**1.7** (0.6 – 5.1)	**1.5** (0.5 – 4.7)

N= actual number of observations, %=weighed percentages, *=p<0.05 comparing to abstainers

† Adjusted for age, sex, marital status, working status, years of education,

‡ Adjusted for all variables included in previous model plus physician's rating of physical health, self-rated presence of chronic diseases and baseline GAD (for incident depression as outcome variable) or baseline Depression (for incident GAD, respectively)

Table 2 Association between different levels of alcohol use at baseline and new onset of Depression/GAD in an international primary care sample separately for males and females

Logistic Regression models§	New onset of Depression				New onset of GAD			
	Males		**Females**		**Males**		**Females**	
percentile range of AUDIT SCORE at baseline	N (%)	OR† (95% CI)	N (%)	OR † (95% CI)	N (%)	OR† (95% CI)	N (%)	OR† (95% CI)
0 – 25th	11 (2.3%)	**1.0**	59 (7.1%)	**1.0**	8 (1.7%)	**1.0**	66 (5.6)	**1.0**
26th – 50th	15 (5.8%)	**2.1** (0.5 – 8.9)	33 (4%)	**0.6** (0.4 – 1.2)	10 (1.8%)	**2.1** (0.4 – 12.1)	30 (3.2%)	**0.7** (0.4 – 1.6)
51st - 75th	3 (0.6%)	**0.2** (0.1 – 1.5)	19 (3.5%)	**0.4** (0.1 – 1.1)	7 (1.3%)	**1.9** (0.3 – 12.2)	19 (2.6%)	**0.9** (0.4 – 2.3)
76th – 90th	10 (1.5%)	**0.7** (0.2 – 3.0)	11 (6.2%)	**1.1** (0.4 – 2.9)	4 (0.6%)	**0.9** (0.1 – 6.2)	7 (1.6%)	**0.4** (0.1 – 1.2)
91st – 95th	9 (3.2%)	**2** (0.6 – 7)	2 (1.7%)	**0.2** (0.1 – 1.3)	7 (2.5%)	**3.8** (0.8 – 17.9)	1 (3.1%)	**0.8** (0.1 – 9.4)
96th – 100th	9 (9.3%)	**2.4** (0.3 – 21.3)	4 (17.2%)	**3.3** (0.7 – 14.8)	6 (4.1%)	**2.5** (0.1 – 41.3)	2 (5.5%)	**0.7** (0.1 – 3.9)

N= actual number of observations, %=weighed percentages,

† Adjusted for age, sex, marital status, working status, years of education, physician's rating of physical health, self-rated presence of chronic diseases and baseline GAD (for incident depression as outcome variable) or baseline Depression (for incident GAD, respectively)

§ using "svy" commands in STATA (see methods)–